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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,706	02/09/2004	Lester F. Lau	05031.0008.NPUS01	2022

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EXAMINER
POPA, ILEANA

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/774,706	LAU, LESTER F.	
	Examiner	Art Unit	
	Ileana Popa	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 September 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,10,16,19 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,10,16,19 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *09 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in the prior Office Action.

2. Claims 5-9, 11-15, 17, 18, and 20 have been cancelled. Claims 1, 10, and 19 have been amended.

Claims 1-4, 10, 16, 19, and 21 are pending and under examination.

Response to Arguments

35 USC § 112, written description

3. The rejection of claims 8, 9, 19, and 20 under 35 USC § 112, first paragraph for failing to comply with the enablement requirement, is withdrawn in response to the cancellation of claims 8, 9, and 29 and in response to the amendment of claim 19 filed on 09/06/2006.

35 USC § 112 - enablement

4. The rejection of claim 20 under 35 USC § 112, first paragraph for failing to comply with the enablement requirement, is withdrawn in response to the cancellation of the calim on 09/06/2006.

5. Claim 19 remains rejected under 35 USC § 112, first paragraph for failing to comply with the enablement requirement for the reasons of record set forth in the prior Office Action. Applicant's arguments filed on 09/06/2006 have been fully considered but they are not fully persuasive.

Applicant traversed the instant rejection on the grounds that claim 19, as amended, is drawn to a screening method wherein the phenotype of the transgenic mouse embryos or of the postnatal mice arising from them is measured only after contacting the embryos with the suspected modulator, obviating the need for *in vivo* testing. Applicant submits that the specification teaches that 65% of the transgenic mouse embryos comprising a heterozygous disruption of the CCN1 gene possess atrioventricular septal defects (AVSDs) of varying severity by E14.5. Applicant asserts that, to identify a modulator, one of ordinary skill in the art contacts a plurality of such embryos or mice arising from them with an agent and then calculates the percentage of embryos or mice possessing at least one phenotype associated with AVSD. Applicant submits that, in paragraph 0032, the specification teaches that embryonic cultures may be used for screening of modulators and that histological analysis may be used to measure said phenotypes. For these reasons, according to the Applicant, the specification enables one of ordinary skill in the art to identify a modulator without undue experimentation. Accordingly, Applicant requests the withdrawal of the rejection.

Contrary to Applicant's assertion, the specification is not enabling for the following reasons:

The instant claim is drawn to a method of identifying a modulator of the development of AVSDs by contacting the transgenic mice with an agent and measuring the phenotypes associated with AVSD in the transgenic embryos or the progeny thereof. Applicant asserts that there is no need for *in vivo* testing because the phenotypes are measured after contacting the embryos with the agent and that the specification enables one of skill in the art to practice the instant invention without undue experimentation. However, the Examiner submits that one of skill in the art would not know how to determine if an agent is capable of changing the phenotype of the embryos in question and of the progeny thereof. First, the specification does not teach any phenotype associated with AVSD, except for cardiac morphological abnormalities identified by histochemistry, i.e., after the embryos or their progeny were sacrificed (paragraphs 0069-0074). Applicant argues that the specification teaches phenotypes associated with AVSD in paragraph 0033. However, paragraph 0033 only teaches that the transgenic mice can be made using the methods disclosed in the specification or methods well known in the art, without disclosing any phenotype. It is noted that the specification discloses that the $CCN^{+/-}$ mice appear to be normal (see paragraph 0029). Therefore, one of skill in the art cannot determine whether a transgenic embryo or progeny thereof develops AVSD without sacrificing the animal. Applicant discloses that only 65% of the transgenic mouse embryos develop AVSD by E14.5, i.e., 35% of the embryos do not develop AVSD, which is a pretty high percentage. For this reason, one of skill in the art would not know than any embryo tested has AVSD before being contacted with the agent and therefore, the fact that the

phenotype is measured after contacting the embryo with the agent might not reflect the reality; the embryo may be one that did not have AVSD to start with. Therefore, it is essential to determine the phenotype for all embryos before they are contacted with the agent. Since the phenotype of the embryos and their progeny can be measured only by histological analysis after they are sacrificed, these embryos or their progeny cannot be used for future studies, i.e., to test whether an agent can modulate AVSD. The Applicant submits that, in paragraph 0009, the specification describes methods for testing AVSD in the transgenic mouse embryos and their progeny, for example Doppler echocardiography. However, paragraph 0009 does teach the use of Doppler echocardiography for human patients. As stated in the prior Office Action, the art discloses that the genetic mouse models for cardiovascular diseases are still awaiting for the development of suitable methods to characterize their phenotype, i.e., the necessity to miniaturize and refine the techniques currently used in larger animals; only these allow for the determination of the cardiovascular phenotypes in the intact, conscious mice (see Fitzgerald et al.).

Given these facts, the skilled artisan would not know *a priori* whether using of a suspected modulator result in altering the phenotype of the $CCN^{+/-}$ embryos or their progeny. One of skill in the art would not know how to determine if a suspected modulator is capable to change the phenotype of the embryos in question. The specification would need to describe examples that specifically address the *in vivo* determination of the phenotype for the same embryo or its progeny before and after contacting them with the test substance. Thus, the specification is not enabling for the

method of claim 19.

Claim Rejections - 35 USC § 102

6. The rejection of claims 1-7 and 10-15, 17, and 18 under 35 U.S.C. 102(b) as being anticipated by Mo et al. (Mol Cell Biol, 2002, 22: 8709-8720) is withdrawn in response to the cancellation of claims 5-9, 11-16, 17, and 18 and due to the amendment to the base claim 1 filed on 09/06/2006.

7. Claims 10 and 16 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mo et al. (Mol Cell Biol, 2002, 22: 8709-8720) for the reasons of record set forth in the prior Office Action. Applicant's arguments filed on 09/06/2006 have been fully considered but they are not fully persuasive.

Applicant traversed the instant rejection on the grounds that (i) claim 10, as amended, is drawn to a method of producing a mouse with AVSD and Mo et al. do not describe the phenotype of the heterozygous mice, nor do they teach a method of identifying such a mouse, and (ii) claim 16 is drawn to a method of identifying a mouse with ASVD and Mo et al. fail to disclose that transgenic mice heterozygous for the disruption of CCN1 gene display ASVD or that testing said mice can be identified. Therefore, the Applicant request the withdrawal of the rejection.

Contrary to Applicant's assertions, Mo et al. teach a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise heterozygous or homozygous disruptions of the CCN1 gene, and testing the transgenic

mice for their genotype (p.8710, column 2, bridging p.8711, Table 1). Although Mo et al. do not mention the phenotype of the heterozygous mice, the heterozygous disruption in the CCN1 gene must necessarily have resulted in the claimed AVSDs, i.e., the phenotype is inherent to the transgenic mice comprising a heterozygous or homozygous disruption in the CCN1 gene. Moreover, Mo et al. teach analyzing β-galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry (p. 8710, column 2, second paragraph) and this would necessarily have resulted in the determination of AVSD, because AVSD is a prominent phenotype that cannot be missed. Therefore, Mo et al. do teach a method ofproducing and identifying a mouse with AVSD by testing the transgenic mouse whose genome comprises a hereozygous disruption of the CCN1 gene for the presence of a phenotype associated with ASVD.

Claim Rejections - 35 USC § 103

8. The rejection of claims 20 under 35 U.S.C. 103(a) as being unpatentable over Mo et al., in view of Christensen et al. (Am J Physiol, 1977, 272: H2513-2524) and Bruneau et al. (Cell, 2001, 106: 709-721), as evidenced by Hickey et al. (Cytogenet Genome Res, 2003, 100: 276-286) is withdrawn due to claim cancellation on 09/06/2006.

9. The rejection of claim 19 under 35 U.S.C. 103(a) as being unpatentable over Mo et al., in view of Christensen et al. (Am J Physiol, 1977, 272: H2513-2524) and Bruneau

et al. (Cell, 2001, 106: 709-721), as evidenced by Hickey et al. (Cytogenet Genome Res, 2003, 100: 276-286) is withdrawn in response to Applicant's arguments filed 09/06/2006.

10. Claim 21 remains rejected under 35 U.S.C. 103(a) as being unpatentable over Mo et al., in view of both Mah et al. (Genet Test, 1999, 3: 157-172) and Ciarleglio et al. (J Clin Invest, 2003, 112: 1280-1286). Applicants' arguments filed on 09/06/2006 have been fully considered but they are not fully persuasive.

Applicants traversed the instant rejection on the grounds that Mo et al. do not teach that CCN1 function plays a role in the development of AVSD and they do not disclose any cardiovascular defect in the transgenic mice comprising a homozygous or heterozygous disruption of CCN1. Applicants argue that Mo et al. do not suggest a correlation between the disruption of CCN1 function and the development of AVSDs and therefore, one of skill in the art would not have been motivated to combine the references. Therefore, Applicants request the withdrawal of the rejection.

As stated in the prior Office Action, Mo et al. teach a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise heterozygous or homozygous disruptions of the CCN1 gene, and testing the transgenic mice for their genotype (p. 8710, column 2, bridging p. 8711, Table 1). Although Mo et al. do not mention the phenotype of the heterozygous mice, the heterozygous disruption in the CCN1 gene must necessarily have resulted in the claimed AVSDs, i.e., the phenotype is inherent to the transgenic mice comprising a heterozygous or homozygous

disruption in the CCN1 gene. Moreover, Mo et al. teach analyzing β-galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry (p. 8710, column 2, second paragraph) and this would necessarily have resulted in the determination of AVSD, because AVSD is a prominent phenotype that cannot be missed. Since Mo et al. teach genotyping the transgenic embryos, they must necessarily teach a method of identifying an animal that is predisposed to ASVD, the method comprising detection of disruption (i.e., alteration) in one or more allele of the CCN1 gene.

New Rejections

Claim Rejections - 35 USC § 112, 1st paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-4 are rejected because a transgenic mouse comprising a suspected modulator of the development of atriovascular septal defects is not enabled by the disclosure. See *In re Mayhew*, 527 F.2d 1229, 188 USPQ 356 (CCPA 1976).

It is noted that the amendments to claims 1-4 introduced new matter. The instant specification does not disclose a transgenic mouse comprising a suspected modulator of the development of atriovascular septal defects and therefore, there is no support in the specification for such a transgenic mouse.

Claim Rejections - 35 USC § 112, 2nd paragraph

13. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

14. Claims 1-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The instant claims are drawn to a transgenic mouse comprising a suspected modulator of the development of AVSDs. It is not clear whether the suspected modulator is a nucleic acid sequence integrated into the genome of the animal or whether the suspected modulator is another type of agent that was administered to the animal. Since the metes and bounds of the claims cannot be determined, the claims are indefinite.

Claim Rejections - 35 USC § 103

14. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and

> the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

15. Claims 1-4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mo et al. (2002, cited on form PTO-892 on 03/07/2006) in view of Lau et al. (PGPUB 2004/0002124).

** The rejection of claims 1-4 is based upon interpretation that a suspected modulator is administered to the animal.

Mo et al. teach a method of producing, identification, and isolation of transgenic mice (and embryos) whose genome comprise a heterozygous disruption of the CCN1 gene, and testing the transgenic mice for their genotype (p.8710, column 2, bridging p.8711, Table 1). Mo et al. do not mention the phenotype of the heterozygous mice. Although Mo et al. do not mention the phenotype of the heterozygous mice, the heterozygous disruption in the CCN1 gene must necessarily have resulted in the claimed AVSDs, i.e., the phenotype is inherent to the transgenic mice comprising a heterozygous or homozygous disruption in the CCN1 gene. Moreover, Mo et al. teach analyzing β-galactosidase expression in heterozygous mice expressed by in situ hybridization and immunocytochemistry (p. 8710, column 2, second paragraph) and this would necessarily have resulted in the determination of AVSD, because AVSD is a prominent phenotype that cannot be missed. Mo et al. do not teach administering agents to their transgenic mice. Lau et al. teach transgenic mice comprising a heterozygous disruption of the CCN1 gene, wherein the transgenic mice are useful as disease models (p. 12, paragraph 0085, p. 39, paragraph 0285). It would have been obvious to one of skill in the art, at the time the invention was made, to use the

transgenic mice of Mo et al. as disease models and try to modulate the disease by treating the mice with suspected modulatory agents, with a reasonable expectation of success. The desire of those of ordinary skill in the art to obtain evidence for the function of genes and identify factors that could alter the pathways in which these genes are involved was well established at the time of filing. The motivation to do so is provided by Lau et al., who teach these transgenic mice as useful as disease model. With respect to the limitation of a suspected modulator of AVSDs, this is not innovative over the prior art because, once the phenotype is identified, one of skill in the art would know to use the proper modulatory agents. Thus the claimed invention as a whole is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

16. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ileana Popa whose telephone number is 571-272-5546. The examiner can normally be reached on 9:00 am-5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave Nguyen can be reached on 571-272-0731. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Ileana Popa, PhD

JANET L. EPPS-FORD, PH.D.
PRIMARY EXAMINER